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Influence of *Helicobacter pylori*- connected metabolic syndrome on non-alcoholic fatty liver disease and its related colorectal neoplasm high risk

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Abbreviations: NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; *Hp*-I, *Helicobacter pylori* infection; MetS, metabolic syndrome; IR, insulin resistance; GM-D, gut microbiota dysbiosis; ACN, advanced colorectal neoplasm; CRA, colorectal adenoma; CRC, colorectal cancer

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To the Editor,

Cho *et al.* (1) concluded that nonalcoholic steatohepatitis (NASH) might be independent risk factor for advanced colorectal neoplasm (ACN) and, considering the sequential progression from colorectal adenoma (CRA) to colorectal cancer (CRC) according to nonalcoholic fatty liver disease (NAFLD) histological spectrum, is an essential message for clinicians. Though further studies are warranted to elucidate the NAFLD pathophysiology associated with ACN, the authors mentioned mediators including insulin resistance (IR) with a proinflammatory state and gut microbiota dysbiosis (GM-D) playing crucial roles in NAFLD pathogenesis resulting in ACN development (1).

Beyond NAFLD, the current worldwide *Helicobacter pylori* infection (*Hp*-I) prevalence is about 58% (varied from 39.9% to 84.2%) with increasing tendency due to immigrants (2); its current prevalence in Asia is about 54.7% (varied from 43.1% to 79.5%) (3). Moreover, GM-D- and/or *Hp*-I- associated metabolic syndrome (MetS) seems to predict NAFLD severity (4); there is a causal relation between GM and MetS and GM-D may play a critical role in NAFLD/ NASH pathogenesis via metabolic and inflammatory pathways. Moreover, GM-D-related MetS may contribute to CRC pathophysiology. *Hp*-I-related MetS is also connected with IR, the pathogenetic key of MetS and its related morbidity, including NAFLD and CRC (2,5).

Based on histology, the practical gold standard for current *Hp*-I diagnosis, our data in 50 CRC patients, 25 patients with CRA and 10 controls, showed significantly

higher presence of *Hp*-I in the CRA (68%) and CRC (84%) groups compared with controls (30%). Regarding the histological severity features in CRA group, presence of *Hp*-I was observed in 50% of patients with mild and 80% of patients with moderate/severe dysplasia (6). Likewise, presence of *Hp*-I in the CRC group was observed in 89% of patients with mild and 83% of patients with moderate/severe grade. Noteworthy, *Hp* presence was documented by immunohistochemical stain in CRA and CRC tissues. In addition, presence of *Hp*-I with accompanying immunohistochemical expression of CD44 -indicator of cancer stem cells and/or bone marrow-derived stem cells in biopsy specimens was found in a high proportion of CRA patients accompanied with moderate/severe dysplasia (88%) and CRC patients with moderate/severe degree of malignancy (91%). Comparable pictures were also obtained for proliferation marker Ki-67, anti-apoptotic Bcl-2 and CD45 (assessing T and B lymphocytes locally) immunohistochemical expressions (6).

Notably, CD44 and CD45 are also NASH key players. More specifically, CD44 increases the hepatic steatosis to NASH progression by controlling hepatic macrophage polarization (pro-inflammatory phenotype) and infiltration, thus making CD44 a possible therapeutic target (7). Moreover, CD44, as a stem cell marker of diverse malignancies, is involved in cancer progression and metastasis, including NAFLD-related hepatocellular carcinoma (8) as well as CRC (9). In this respect, one could hypothesize that CD44 might also be involved in NAFLD-related CRC progression and metastasis (10), and thus further studies are needed to elucidate this field.

Therefore, because active *Hp*-I with concomitant NAFLD, MetS and/or other MB-D, might be involved in CRA-CRC sequence, *Hp* eradication might benefit these pathologies and thus large-scale studies are required.

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